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1.

INTRODUCTION TO PHARMACOLOGY, AND ROUTES OF DRUG ADMINISTRATION AND ABSORPTION

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Contents

Summary This eChapter has an introduction to pharmacology and drug nomenclature followed by a detailed discussion of routes of administration starting with oral administration (with absorption from the gastrointestinal tract, and first pass liver metabolism. This is followed by a discussion of rectal, sublingual and injection routes of administration (intravenous, intra-arterial, subcutaneous, intramuscular, intrathecal and epidural). Then the topical, pulmonary and intraosseus routes of administration are considered.

1.1 Introduction to Pharmacology

Pharmacology is the study of all aspects relating to drugs or medicines. Some of us, use the term 'drugs' to cover medicines (prescription and non-prescription) and drugs of abuse (legal and illicit), and this is how I am going to use 'drugs' in this Unit. The popular press often uses the term 'drugs' to mean drugs of abuse, and this can be confusing. Some medicines can also be drugs of abuse, which further complicates the issue. For example, morphine is both a potent pain reliever and a drug of abuse.

There are a huge number of drugs available in Australia. Currently there are 27,000 drugs on the Australian Register of Therapeutic Goods (ARTG) and, of these, 3,500 are registered as prescription only.

Pharmacology can be divided into two parts; **pharmacokinetics** and **pharmacodynamics**.

Pharmacokinetics is '**What the body does to the drug'**. After administration, the drugs usually has to be absorbed into the body, may be distributed around the body, and/or metabolised, and will eventually be excreted/eliminated. Absorption (A), distribution (D), metabolism (M) and excretion/elimination (E), sometimes referred to as ADME, are all pharmacokinetic processes and they may be altered in disease states. This is important, as we most commonly use drugs in disease states.

Pharmacodynamics is **'What the drug does to the body'**. When we administer a drug to a person, we hope that the drug will have a beneficial effect. In order to do so, the drug will have to cause an alteration in a physiological, biochemical or pathological process. This alteration is called the mechanism of action or pharmacodynamics of the drug. It is the molecular mechanism of action of the drug, and the actions of the drug in the human body that follow from this mechanism of action.

Pharmacokinetics and pharmacodynamics are related, as shown in Figure 1.1.

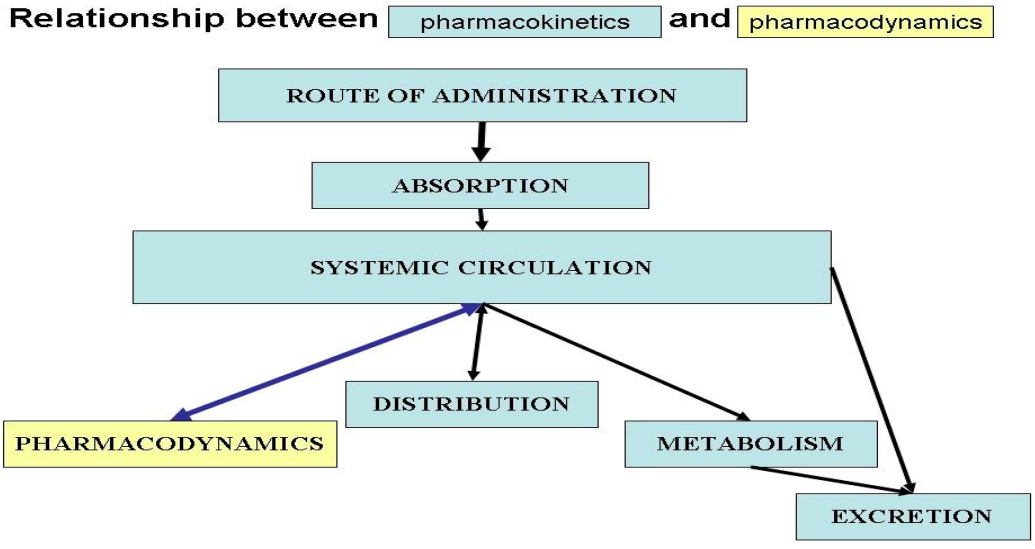

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Figure 1.1 Relationship between pharmacokinetics and pharmacodynamics (Copyright QUT, Sheila Doggrell)

Pharmacokinetics includes ADME; Absorption, Distribution, Metabolism and Elimination. After administration, drugs undergo **absorption** into the systemic circulation, this is the

circulation that takes blood to most parts of the body, and will take the absorbed drugs with it. Drugs can be further **distributed** into tissues or fat, and may also be released back into the circulation from the tissues and fat. Drugs are often targeted to have actions at specific sites, and when the drug reaches this site, the process of pharmacodynamics starts. Pharmacodynamics is a change in the body system – hopefully for a beneficial effect. After having an effect, the drug often returns to the circulation, where it will be taken in the circulation to its site of **metabolism**, which is commonly the liver. After metabolism drugs are removed from the body by **excretion**, commonly from the kidney. Some drugs are not metabolised but are directly eliminated via the kidneys.

In addition to pharmacokinetics and pharmacodynamics, there are some other pharmac…..terms used in pharmacology. The first is **pharmaceutics**, which has some overlap with pharmacokinetics. **Pharmaceutics** is designing formulations of drugs suitable for administration to people. **Pharmacogenetics** is the genetic basis for variation in drug response. This variation can have a basis in pharmacokinetics or pharmacodynamics, and we will discuss examples of these later. **Pharmacovigilance** is the detection, assessment, understanding, and prevention of adverse drug effects and adverse drug interactions. Some of these adverse effects and adverse drug interactions are at the level of pharmacokinetics and some at the level of pharmacodynamics. Examples of pharmacovigilance will be discussed later.

1.2 Drug Nomenclature

An important issue to learn about at the start of a Unit in pharmacology is **drug nomenclature**. When I tell people that I am a pharmacologist, people often respond by saying "I'm taking Tenormin for my hypertension – do you know anything about this drug?" Tenormin is a tradename, and pharmacologists do not use trade names. So, I usually reply that "Tenormin is a tradename, and I can't tell you anything about it unless you give me the real name of the drug". Tenormin is actually **atenolol**, a β-blocker commonly used in the treatment of hypertension, and I know a lot about atenolol.

Each drug actually has 3 names. The first is the chemical name, and is the name used by chemists to describe the chemical structure. The second name is the generic, and this is the one used by pharmacologists. The generic name is also known as the non-proprietary name to distinguish it from the proprietary or trademark name. The trade name is used by the pharmaceutical companies. To give an example: the chemical name for diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-,1,4-benzodiazepin-2-on, and from this name, a chemist could draw the structure. The generic name is **diazepam**, which is a commonly used sedative. The third name is the proprietary or tradename. Each company can have a different tradename (brand name) for the same drug, the best known proprietary or tradename for diazepam is Valium (from the pharmaceutical company Roche), but other proprietary names for diazepam include Valpam (Arrow), Antenex (Alphapharm) and Ducene (Sauter). Thus, there are at least 4 different trade names for the same drug. Pharmaceutical companies probably like the use of their tradename, as this gives them some free advertising. However, it is more correct (and less confusing) to use generic names. Generic names are used throughout this Unit and eBook.

1.3 Introduction to drug administration and absorption of drugs

The first step in pharmacokinetics is the administration and absorption of drugs. The chemical structure and nature of a drug may determine which route of administration can be

used for? a drug. Drug absorption depends on the route of administration. When a drug is administered into the mouth (orally), absorption will be from the gastrointestinal tract. However, if a drug is administered into a vein (intravenously), absorption will be from the circulation.

1.4 Routes of drug administration

The routes of drug administration are described as **enteral**, which means into the gastrointestinal tract, or **parenteral** (not into the gastrointestinal tract). Routes that are enteral (into the gastrointestinal tract) are **oral** and **rectal**. Routes that are parenteral include **sublingual** (under the tongue) and **injection**, which can be to a variety of sites e.g. into the vein (**intravenous**), into the muscle (**intramuscular**), under the skin (**subcutaneous**). Other parenteral routes include **topical**, which is to a body surface, such as the skin, nose, eyes etc. and **pulmonary**, which is delivery to the lungs. These routes of drug administration are considered in sequence. The route of administration used for a drug may also depend on whether a systemic (around the body) effect is required. Local administration is a way of trying to limit the effects of a drug to a local area.

1.5 Oral administration, absorption from gastrointestinal tract, and first pass liver metabolism

The oral route of administration is the most convenient: subjects prefer to take an oral preparation rather than have an injection, or rectal administration. Oral administration is also the safest. For instance, we have more time to reverse the effects of a drug administered orally than when it is administered directly into a vein. Oral is the most commonly used route of administration. Oral administration usually gives systemic effects (around the body) rather than local effects of drugs. Thus, after oral administration, a drug ends up in the systemic circulation being widely distributed to tissues and organs, with the possibility of having a widespread effect.

A disadvantage of oral administration can be the slow onset of action, as the drug has to be absorbed and taken to its required site of action before it can start to have an effect. In an emergency, drugs that are active after oral administration, may be given intravenously to speed up their onset of action. If the patient is vomiting, the drug may never reach the intestine to be absorbed. Thus, when the patient is vomiting, oral is not an appropriate route of drug administration.

Oral preparations can take several forms. **Tablets** are compressed powder, often with starch added to swell when in contact with fluids, to aid dissolution (breakdown of the tablet). Capsules contain a shell of gelatine, which is a tasteless natural substance. **Hard gelatine capsules** contain the drug as solid, whereas **soft gelatine capsules** contain drug as an oily liquid. Capsules are often preferred to tablets as they disguise the taste. For instance, the antibiotic **amoxycillin** is given in capsule form to prevent its bad taste upsetting the subject. Children often have problems swallowing tablets or capsules. If swallowing is a problem, **oral liquid preparations** can be used.

The gastrointestinal tract is designed to handle food and fluids not drugs. Drugs piggyback on the physiological processes to handle food. Also, the physiological processes that normally impact on food and fluids, can affect drug delivery. For instance, the digestive enzymes that breakdown proteins in the diet, can also breakdown some peptide drugs e.g. **insulin**. Thus, when insulin is being used to treat diabetes, it is not administered orally. The absorption of some drugs is inhibited by forming complexes with components of the diet e.g. the **tetracycline** antibiotics form non-absorbable complexes with calcium (dairy products).

Some drugs irritate the lining of the gastrointestinal tract to cause emesis (vomiting), and such drugs cannot be used orally e.g. some of the cytotoxic (cell killing) anti-cancer drugs.

The processes that need to happen to get drug delivery from the gut into the circulation are given in Figure 1.2. Firstly, the drug has to be **released** from the dosage form (tablet or capsule). Secondly, the drug has to separate and/or dissolve; this is called drug **dissolution**. After dissolution most drugs are absorbed by simple **diffusion**, although a few drugs are **transported** by physiological processes.

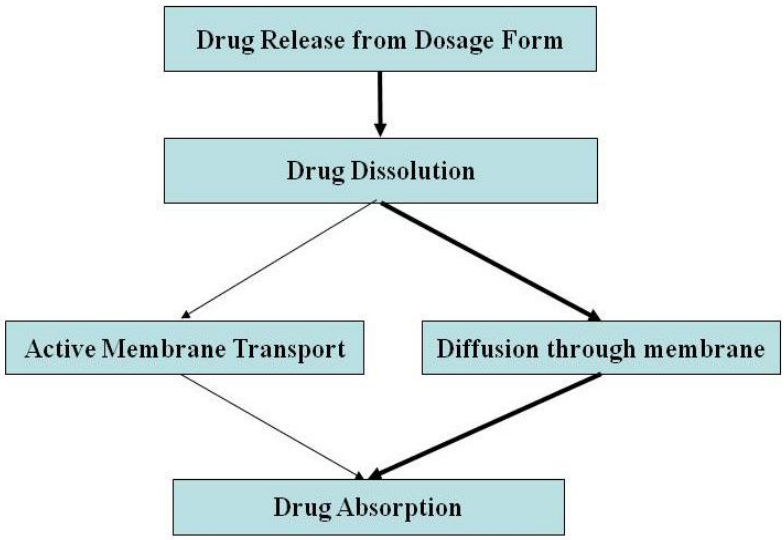

Figure 1.2 Processes to get drug delivery from gut (Copyright QUT, Sheila Doggrell)

The body has many **membrane transporters**. These are like being transported by a bus; they pick up drugs and take them to their destination across membranes. For instance, after the proteins have been broken down to amino acids, the amino acids are absorbed by active transport across the gut membrane. Drugs with similar structures to the natural substrates (substances) for these transporters can use these transporters. For instance, **thyroxine**, which is commonly used in the treatment of hypothyroidism, uses the physiological transporter for amino acid absorption. Another example is the drug **L-dopa**, which is used in the treatment of Parkinson's disease. L-dopa is a naturally occurring compound, and has its own transporter.

The most common method for drug absorption is **diffusion**. As cell membranes are lipid, to diffuse through the lipid cell membranes, drugs must be lipid soluble (**lipophilic**). 'Philic' means likes, whereas 'phobic' means does not like. Drugs that are not water soluble (**hydrophobic**) are often lipophilic, and absorbed by diffusion. In contrast, water soluble drugs (**hydrophilic**), which are not lipid soluble (**lipophobic** drugs; e.g. **curare**), are not well absorbed after oral administration.

The case of curare tells us a lot about routes of drug administration. Curare was used on the tips of the arrows of South Americans to kill animals. Once the curare was injected into the animal, it became paralysed. However, when the South Americans ate the curare-injected animals, they were not paralysed. This is because curare is a strong base and not absorbed from the gastrointestinal tract, so has no effect after oral administration. However, it is

absorbed after intramuscular injection to give its muscle relaxant effect. Curare is still used today to cause muscle relaxation during operations. In addition to strong bases, strong acids are poorly absorbed after oral administration, and have to be given by another route.

Strong acids and strong bases (e.g. curare) are not absorbed. Thus, drugs are usually designed to be weak acids (e.g. **aspirin**) or weak bases (e.g. **morphine**), as these are more lipid soluble and readily diffuse through the gastrointestinal cells membranes. Weak acids are lipophilic at low pH (which occurs in the stomach) and are capable of being absorbed from the stomach. In contrast, weak bases are lipophilic at high pH (in the intestine), and are absorbed from the intestine.

The stomach is acidic, with a pH of 1-3, compared with the small intestine, which has a pH in the range 5-8. Acidity is increased at night, and this may increase the absorption of some drugs. In contrast, **antacids** decrease the acid in the stomach, and can inhibit the absorption of some drugs. As the acidity in the stomach leads to the association of weak acids, some of these are absorbed from the stomach. However, the stomach is not designed for absorption, and most absorption occurs in the small intestine, which is designed for absorption with villi (projections) and microvilli giving a large surface area.

Drugs will reach the small intestine more rapidly, if administered with water to a patient, whose stomach is empty of food. If a drug is absorbed lower down the gut, the volume of gastric contents will determine the delay before absorption starts. Gastric contents are not the only determinant of rate of gastric emptying and, hence, drug absorption in the intestine. Gastric emptying rate is **slowed** by diet, especially a diet containing fatty foods or a high bulk diet. Diseases of gastrointestinal tract, such as gastric ulcers or pyloric stenosis, can slow gastric emptying. Gastric emptying is also slowed during pregnancy. Certain drugs (e.g. **anti-muscarinics**) and alcohol also slow gastric emptying. Indeed, one of the uses of antimuscarinics is to slow gastric emptying in dysentery. With slow gastric emptying, there is more time for the breakdown of drugs by the enzymes and/or acid in the stomach, and this means the subsequent levels in the blood may be lower.

Gastric emptying rate is **promoted** by hunger, anxiety and certain drugs (e.g. **metoclopramide**). Increased gastric emptying may promote the absorption of any drug, and lead to increased blood levels. Metoclopramide is not used to promote gastric emptying but as an anti-emetic (prevention of nausea and vomiting). During this use of metoclopramide, there may be higher blood levels of other drugs being used at the same time.

The small intestine is the primary site of drug absorption. The longer the drug remains in the small intestine (residence time), the greater the absorption of the drug from the intestine. However, some drugs are metabolised and inactivated by the intestinal mucosa e.g. **progesterone**, which means they are not very effective after oral administration. Thus, orally active **progesterone-like** drugs, designed to be active after oral administration, are part of the oral contraceptive, rather than progesterone itself.

Prodrugs are compounds that are metabolised to active drugs in the body. Some prodrugs rely on degradation in the intestine to release the active drug. For instance, erythromycin stearate is metabolised to provide the antibiotic **erythromycin.**

Drugs may have a short action if their dissolution and absorption in the gastrointestinal tract is too quick, or metabolism is too quick. This may mean that a drug has to be taken often, say every 2 or 3 hours. People are not very good at remembering to take drugs every 2 or 3 hours, especially during the night, and with such regimens, people miss doses; their

adherence to the dosage regimen is low. For this reason, it is best to formulate drugs so that they only need to be taken once or twice a day. To achieve this **controlled/slow (sustained) release preparations** have been developed. These have a slowed rate of dissolution in the gastrointestinal tract allowing them to be used less frequently and/or allowing the maintenance of a therapeutic effect overnight. For instance, the use of **nifedipine** in the treatment of hypertension was initially not very effective as nifedipine is rapidly metabolised, and therefore has to be taken frequently, which patients find difficult to adhere to. With **nifedipine SR**, there is a slower dissolution of the tablet, and prolonged delivery, which allows nifedipine SR to be used twice a day, so nifedipine SR allows a more effective control of blood pressure.

Some drugs are ineffective when administered by the oral route as they are destroyed by the acid in the stomach e.g. **erythromycin. Enteric-coated preparations** are designed to prevent destruction by acid in the stomach, and this allows some of the drug, which would otherwise be destroyed by acid, to be effective after oral administration**.** The antibiotic **erythromycin** can be used in an enteric-coated preparation.

An important term that is often used in association with the use of medicines is **bioavailability**. Bioavailability is the fraction of an ingested dose of a drug that gains access to the systemic circulation. To reach the circulation (see Figure 1.3), drugs must penetrate the intestinal mucosa and avoid metabolism by the intestinal and liver enzymes. Drugs that reach the blood vessels of the gastrointestinal tract are carried in the blood supply directly to the liver by the portal vein. The liver is a major source of enzymes, and these enzymes are involved in the biochemical processes in the body. While, none of these enzymes have drugs as their natural substrates, they do metabolise drugs. Indeed, many drugs are inactivated by metabolism. After oral administration, drugs cannot avoid being taken to the liver. Metabolism after absorption from the gut is known as **First Pass Metabolism**. If drugs undergo extensive **first pass metabolism** after oral administration, they are often administered by another route to avoid this inactivation e.g. sublingual, rectal.

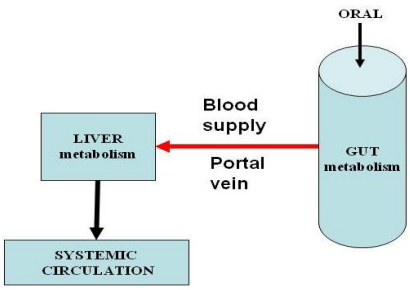

Figure 1.3 First pass metabolism (Copyright QUT University, Sheila Doggrell)

Whether drugs are administered orally or by other routes, they often end up in blood vessels, and, to reach their target site, have to then be **absorbed from blood vessels**. This occurs predominantly by diffusion. Cardiovascular disease can lead to low perfusion of tissues (e.g. in heart failure, there is low perfusion of tissues) and this can slow the absorption of drugs. Conversely, exercise increases blood flow, and will increase the absorption of drugs from the blood vessels in skeletal muscle.

In addition to oral administration, routes of drug administration include sublingual, rectal, injection, topical, and pulmonary. Each of these routes has both advantages and disadvantages when compared to oral administration.

1.6 Sublingual

Extensive first pass liver metabolism makes it difficult to administer some drugs by the oral route. **Sublingual** (under the tough) administration can be used to avoid first pass liver metabolism. Drugs that are absorbed via the oral mucosa drain into the superior venae cavae to the heart and systemic circulation; they are not transported directly to the liver, and thus do not undergo first pass liver metabolism. Once in the systemic circulation, only part of the drug will pass through the liver with each circulation - the rest will go through other organs or tissues, which may not metabolise the drug to destroy it: Figure 1.4.

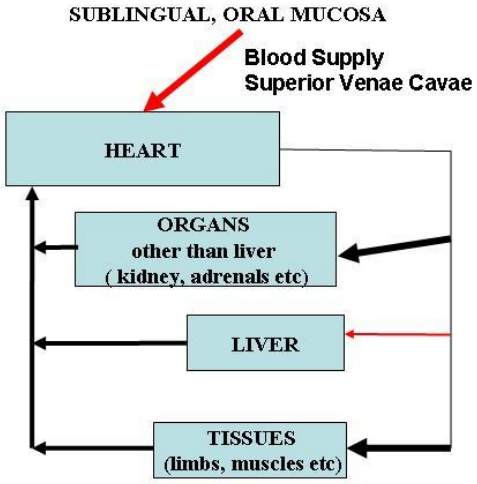

Figure 1.4 Sublingual drug administration (Copyright QUT University, Sheila Doggrell)

The sublingual route of administration increases the bioavailability of drugs that are extensively metabolised by the liver. The best known example of a drug that is used sublingually to avoid first pass liver metabolism is **glyceryl trinitrate (nitroglycerin)**. Oral nitroglycerin is ineffective as it is extensively metabolised by the liver, and little enters the circulation if taken orally. In an attack of angina, nitroglycerin administered sublingually does get into the circulation, and rapidly provides relief from the attack of angina.

1.7 Rectal

The rectum is at the end of the large intestine, and is about 15-20 cm long. Drugs are specially formulated for rectal administration, and the Solid Drug Formulations for Rectal Use are known as **suppositories**.

Rectal administration avoids first pass liver metabolism. This is because, after insertion into the lower part of the rectum, absorption is into rectal veins and then into the general circulation. As the absorption is not into the portal vein, this avoids first pass metabolism. Another advantage of rectal administration is that the rectum has little enzymatic activity, and this route avoids upper gastro-intestinal acids and enzymes, which destroy many drugs. Rectal administration may be useful in the presence of upper gastrointestinal disease, which affects the absorption of the drug given via oral administration.

Rectal administration can be useful when oral administration is not possible. For instance, in nausea and vomiting, or in subjects who have difficulty in swallowing, oral administration is not possible. Post-operative vomiting prevents oral administration, but drugs can be administered rectally to reach the circulation to be effective. In children in status epilepticus, it is not possible to get the child to swallow, but rectal **diazepam** can be used to control the epilepsy. The major disadvantage of rectal administration is that it is not popular with people.

In addition to being used to achieve systemic effects, the rectal route can also be used to give a local effect. For example, suppositories can be used in the treatment of haemorrhoids.

Suppositories and enemas are different. **Enemas** contain hypertonic solutions that draw water to them to produce a laxative effect, and are used in subjects with constipation.

1.8 Injection

There are mainly sites that drugs can be injected into, and the absorption will be different from each of these sites. The sites include **intravenous** (into the vein), **intra-arterial** (into the artery), **intradermal** (into the dermis layer of skin), **subcutaneous** (under the dermis, in the subcutaneous tissue), i**ntramuscular** (into the muscle), i**ntrathecal** (into the cerebral spinal fluid), and e**pidural** (into the epidural).

1.8.1 Intravenous

Injection into a vein (**intravenous**) relies on the skill of finding a vein, getting a needle into the vein, and keeping the vein open during the injection. This is a skill that relies on practice at the patient's expense! One of the major advantages of the intravenous (i.v.) route is that it gives more immediacy and accuracy than other routes. Immediacy may be required in an emergency situation. Thus, when a subject has intense pain, quick pain relief is required. **Morphine** is a potent analgesic (pain reliever). For quick pain relief, morphine is administered intravenously, and pain relief occurs in 10-15 minutes, whereas if morphine is administered orally, to takes 30 minutes to cause pain relief.

After oral administration, in addition to the time lag for absorption, there may be a reduction in drug activity by liver metabolism, which gives a range of bioavailability, which is specific for each drug. In contrast, intravenous administration avoids first pass liver metabolism, allows for a rapid effect, and the bioavailability is 100%. Because of the greater bioavailability after intravenous administration, a lower dose may be required after intravenous administration than oral administration. For instance, when the pain killer **pethidine** is administered orally, the dose is 100 mg, and there is extensive first pass liver metabolism. When pethidine is administered intravenously, there is no first pass metabolism, and the dose is 25 mg.

The intravenous route of administration can be used for drugs that are not active after oral administration e.g. ionised drugs, peptides. The intravenous route of administration can often be used for drugs that irritate the intestinal mucosa, as blood vessel walls are quite insensitive. Many of the **cytotoxic** (cell killing) **anti-cancer drugs** irritate the intestinal mucosa but not the blood vessels walls, and are given intravenously

One disadvantage of the intravenous route is that it is not suitable for all drugs. Drugs in oily vehicles or drugs that precipitate blood constituents or haemolyse red blood cells cannot be used intravenously. Another disadvantage of the intravenous route is that, with oral administration of the wrong drug or the wrong dose of a drug, there is an opportunity to remove the drug during absorption, and before it reaches the circulation, but this is not

possible after intravenously administration. Thus, it is a disadvantage that the actions of an intravenously administered drug are often not easily reversed.

1.8.2 Intra-arterial

The main disadvantage of **intra-arterial injection** (injection into an artery) is that it requires great care, and should only be done by experts. If you get it wrong, there will be blood everywhere! Intra-arterial (i.a.) injections are used to localise effects of a drug to a particular tissue or organ e.g. in the treatment of renal tumours or head/neck cancers, drugs can be injected into the renal artery or carotid artery, respectively. After intra-arterial administration, the highest concentrations are localised and have their maximum effect locally. As the drug moves away from its site of injection, it is diluted in the circulation, and this reduces the toxicity of the drug. Another advantage of intra-arterial injection to the site of action is that it avoids first pass liver and lung metabolism.

1.8.3 Subcutaneous

Subcutaneous is injection of a drug under the skin. An advantage of subcutaneous (s.c.) administration is that it avoids first pass liver metabolism, as the drug is released into the circulation, rather than specifically into the portal vein. From the subcutaneous area, absorption is often by diffusion. The drug is administered in a depot under the skin with absorption into plasma, and then to the circulation often sufficiently constant and slow to provide a sustained effect. Thus, subcutaneous administration can provide a slow release preparation for ongoing effects. Also, the rate of absorption after subcutaneous administration can be varied. For instance, in diabetics, **soluble insulin** with rapid absorption can be injected subcutaneously to mimic the rapid rise in blood insulin observed with a meal. Whereas an **insoluble suspension of insulin** can be used for the slow absorption required to give the low constant fasting level of insulin.

The area affected by the subcutaneous administration of a drug can be limited by the injection of a vasoconstrictor (e.g. **adrenaline**) with the drug. The localised vasoconstriction response to adrenaline limits the transport of the drug away from the site of injection in the circulation.

This method is used with **local anaesthetics** to keep the effect of the anaesthetic confined to a local area. Without a vasoconstrictor, the local anaesthetic and the anaesthetic effects spread from the site of injection, and are no longer local.

1.8.4 Intramuscular

Intramuscular is injection into the muscle. An advantage of **intramuscular** (i.m.) administration is that it avoids first pass liver metabolism, and it may be suitable for drugs that undergo extensive first pass liver metabolism. The intramuscular route is often suitable for drugs that are mucosal irritants or drugs that are irritants after subcutaneous injection.

Drugs in aqueous solution are absorbed quite rapidly from muscle, but the rate of absorption will depend on the rate of blood flow at the injection site. If the blood flow is high, the rate of absorption will also be high. The rate of absorption of an aqueous solution is greater from the deltoid (shoulder muscle) or vastus lateralis (above the knee muscle) than from the gluteus maximus (butt muscle). Absorption from gluteus maximus is particularly slow in females who have more subcutaneous fat in this area than males, because fat slows the absorption. **Gardasil,** the vaccine designed to prevent most cases of cervical cancer, is injected into the deltroid for quick absorption.

Blood flow to the legs is increased during jogging. If **insulin** is injected into the leg, rather that into the arm or abdominal wall, as recommended, it is absorbed quickly during jogging.

With higher levels of insulin than expected, there is an increased take up of glucose into the tissues, which can cause an unwanted major drop in blood glucose leading to an episode of hypoglycaemia.

1.8.5 Intrathecal

Intrathecal is injection into the cerebral spinal fluid. This is a method for direct delivery of a drug to the central nervous system. Intrathecal is used with **local anaesthetics** to give spinal/regional anaesthesia, often prior to perform operations on low limbs.

The opioid μ-receptors that mediate pain are in the spinal cord. Drugs that are administered to the cerebral spinal fluid are being delivered to this site of pain mediation. Thus, the intrathecal route of administration can be used with the opioid antagonist **morphine** to give good pain relief.

1.8.6 Epidural

An epidural is an injection into the epidural, which is the area above the dura mater, the layer before the cerebral spinal fluid. The best known example of epidural injections is when used with **local anaesthetics** during childbirth to prevent the pain associated with childbirth.

1.9 Topical

Topical administration is to the surface, and is used to give local effects. Topical administration avoids first pass metabolism. However, drugs that are absorbed into the circulation after local administration may then have systemic effects.

The topical surface can be **skin** or **mucous membranes**, and these have different properties. Mucous membranes used for drug administration include those of the conjunctiva (eye), nasopharynx (nose), oropharynx (throat), vagina, urethra, and urinary bladder. Absorption from these mucous membranes occurs readily. Topical administration to the skin and selected mucous membranes are discussed below.

1.9.1 Skin

Topical administration of drugs to the skin usually uses **patches** or **ointments**, which are applied to the skin. The outer layer of the skin (the epidermis) is a lipid barrier, and aqueous solutions will only be absorbed slowly. If necessary, absorption can be enhanced by suspending the drug in an oily substance and rubbing the resulting preparation into the skin. The epidermis is the main determinant of the rate of absorption from the skin, as the inner layer of the skin (the dermis) is freely permeable. Avoidance of first pass liver metabolism is a major advantage with administration. Thus, drugs that undergo extensive first pass liver metabolism can be used topically. For instance, the **nitrates** can be given in patches that provide long term release and long term prevention of angina. The nitrates have their effect on blood vessels, and thus require absorption into the systemic circulation to be effective.

However, topical administration can be also be used to produce local effects and avoid systemic effects/side effect, when this is required. The anti-inflammatory **glucocorticoids** can have severe adverse effects if they get into the blood stream. However, they can be used safely in skin diseases with local application. Topical administration to the skin provides the highest concentrations of glucocorticoids, and the majority of their effects at the required site (the skin). Only low concentrations of the glucocorticoids will enter the systemic circulation with the potential to cause adverse effects.

Controlled-release preparations for topical administration to the skin are increasing being used to give a long term steady state level of drug. For instance, **nicotine patches** are

controlled-release preparations that help to reduce cravings in smoking cessation. Another example is the s**copolamine patche**, which is a slow release preparations to prevent motion sickness.

1.9.2 Nasal mucosa

The nasal mucosa is highly porous and permeable to drugs. The nasal mucosa is highly vascularised. The nasal mucosa also has a relatively large surface area as a result of microvilli on the epithelial cells, and this aids absorption from the nasal mucosa. One disadvantage to the nasal route is that the drug may be rapidly removed by a runny nose. Thus, it is an unreliable route of administration in subjects with a cold or hayfever.

Occasionally peptide drugs are given nasally for systemic effects. This is because the nasal route avoids gut digestion by gastro-intestinal enzymes and first pass metabolism. The peptide **calcitonin** is administered nasally when it used for its effects in preventing further bone loss in the treatment of osteoporosis. However, most of the drugs that are commonly administered intranasally are those with effects on the nose. For example, **decongestants** are administered to the nose, when it is congested in a cold.

1.9.3 Eye

When a drug is a liquid/**drop form**, it is placed on the conjunctiva, and the released drug dissolves in the tears, and following blinking, is distributed to the site of absorption, the cornea. Local effects usually require absorption of the drug through the cornea. Although eye drops are used for their local effects, absorption can lead to systemic effects as the drug is drained from the eye through the nasolacrimal canal. As this drainage is not subject to first pass liver metabolism, it can lead to systemic side effects. Absorption may be increased by corneal infection or trauma, and dosage and care is needed in these conditions. An example of a drug that is used as eye drop is the β-blocker **timolol**, which is used in the treatment of glaucoma, high intraocular pressure. The highest concentration of timolol is in the eye, and that is where the predominant effects are. Major systemic effects are not observed after timolol is applied topically to the eye.

Drugs can also be administered to the eye in the form of an **ointment**. A small amount of ointment is put along the inside of the lower eyelid. Then, blinking will spread the ointment over the cornea, and the drug will be absorbed. This provides a more prolonged contact time with the cornea, and more prolonged absorption. With ointments, the application to the eye is less often than with drops.

1.9.4 Vaginal

Suppository-shaped medications are available for vaginal administration. These are known as **pessaries**, and are designed to obtain a local effect. An example of a drug used in a pessary is **clotrimazole**, an anti-fungal drug for the treatment of vaginal candidiasis (thrush).

1.10 Pulmonary – Inhalation

Drugs used for effects on the pulmonary system are often administered by inhalation to give the highest concentrations of the drug in the lung. The human respiratory tract has a considerable surface area, which should aid absorption, but most of this is deep in the alveolar region of the lung and it is difficult to deliver drugs deep into the lung. Inhalation is not actually a very good way of delivering drugs to the lung, as only about 10% of a drug that is inhaled actually goes to the lungs, the rest is swallowed, and may be absorbed from the gastrointestinal tract.

With inhalation, predominant **local effects** are achieved in pulmonary diseases (e.g. bronchial asthma) by having the highest concentration of the drug in the lung. In asthma, **metered-dose inhalers** are used. These have an inert propellant gas, and require good hand-breath co-ordination to achieve inhalation, rather than swallowing. An example of a drug that is used in a metered-dose inhaler is s**albutamol** for the treatment of bronchial asthma. Another way to deliver drugs to the airways is to use a **nebulisers**. Nebulisers produce fine droplets in the air (aerosol), and are used to deliver large doses of drugs in an emergency. Thus, in the emergency treatment of asthma, large doses of **salbutamol** can be delivered by a nebuliser.

Local pulmonary effects can be achieved by using drugs that are poorly absorbed. For example, the glucocorticoid **beclomethasone** is poorly absorbed from the pulmonary epithelium in bronchial asthma. Thus, it remains in the lung to have an anti-inflammatory effect in asthma. Localised pulmonary effects without major systemic adverse effects can also be achieved by inhaling drugs that undergo extensive liver metabolism. For example, after inhalation, the glucocorticoid **budesonide** has anti-inflammatory effects on the lung. As **budesonide** is rapidly metabolised by liver this prevents it from having serious systemic adverse effects.

After inhalation, when a drug is deep into the lung, access to the circulation is rapid because the lung has a large surface area. Thus, inhalation can also be used for **widespread effects**, including central effects. For instance inhalation is used for **gaseous** and **volatile anaesthetics**, which are rapidly absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract, and have their anaesthetic effect within the central nervous system.

Methoxyflurane was introduced as an inhalation anaesthetic, but was withdrawn because of toxicity. Lower less toxic doses of methoxyflurane are analgesic and are used for the treatment of acute pain in the emergency situation. The analgesic effect of methoxyflurane is mediated by the central nervous system.

1.11 Intraosseous

Intraosseous is into the bone marrow. The bone marrow is highly vascular, which means that drugs injected into the bone marrow are rapidly circulated. The needle injection is through the outer bone layer to the soft marrow interior. The injection is usually done just below knee. Intraosseous is not the first choice for drug administration. It is usually only done after two attempts at inserting a line to do an intravenous infusion have failed. Examples of when intraosseous can be used include, a child 5 years or younger who is unconscious, unresponsive and in immediate danger of dying. Intraosseus is also used when cardiopulmonary resuscitation support is required, and this is for patients of all ages, and in circulatory shock treatments where there is collapse of the circulation making cannulation difficult.